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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/064,057	04/22/1998	GARY F. GERARD	0942.4330002	5386

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EXAMINER
NASHED, NASHAAT T

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/064,057	Applicant(s) Gerard et al.
	Examiner Nashaat T. Nashed	Art Unit 1652

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 9, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26, 28, 33, 117-125, and 127-148* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26, 28, 33, 117-125, and 127-148* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *40*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The application has been amended as requested in the communication filed September 9, 2002. Accordingly, claims 39 and 40 have been canceled, claims 26, 28, 33, 117-123, and 127-148 have been amended.

Claims 26, 28, 33, 117-125, and 127-148 are pending and under consideration in this Office action.

Applicant's affirmation of their election of AMV reverse transcriptase in Paper No. 44 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures for the reasons set forth in the prior Office action, paper number 41.

In response to the above objection to the specification, Applicants filed new sequence listing in paper form and a computer readable form and traverse the objection on the ground that the application in compliance with the sequence rule because sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section according to 37 C. F. R. § 1.821.

Applicants' arguments filed 9/9/03 have been fully considered but they are not deemed to be persuasive. Reverse transcriptases and the nucleic acids encoding them contain more than four amino acids and 12 nucleotide, respectively. The specification discusses several specific mutants of some reverse transcriptases at specific amino acid residues without identifying the amino acid sequence from which those residues are from. For example on page 57, the text indicates the mutation of Asp-450 to Ala, Glu-484 to Gln, and Asp-505 to Asn, presumably, from an RSV-reverse transcriptase without identifying the amino acid sequence by a sequence identification number. Clearly, the specification in this instant example and others is discussing a specific amino acid sequences containing at least 505 amino acid residues, i. e., more than 4 amino acid residues, from which a specific amino acid residues are selected for mutation. Another examples of improper disclosure of specific amino and nucleic acid sequences is found on page 73, lines 13-15. Referencing a specific amino/nucleic acid sequence by an accession number in commercial data base is improper since the data base may change the accession number without referencing the old number. Thus, the specification fails to comply with

the sequence rule. Applicants are required to perfect their compliance with the sequence rules.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28, 33, 117-125, and 127-148 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons set forth in the prior Office action, paper number 41.

Applicants argue that the claimed invention is fully described in the specification and referenced the specification at page 22, lines 11-16 and pages 69-76 and 106, and indicated that the AMV RT α gene (presumably a wild-type) and AMV RT β gene (a mutant corresponding to the AMV RT β gene mutated to minimize the RNaseH activity). They further argue that polymerase units of activity are well known in the prior art are well known in the prior art and described in the specification on pages 63 and 99.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. First, if the deposit is perfected, the lack of written description rejection against claims directed to the wild-type homo- and heterodimer AMV-RT as well as the specific mutant of the deposited mutant of AMV-RT would be vacated. In order to perfect the deposit, one of the following is required:

(1) If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by the applicant, or a statement by an attorney of record over his/her signature and registration number, stating that the specific microorganism has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

(2) If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. § 1.801-1.809, the applicant may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his/her signature and registration number, showing that:

(1) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(2) all restriction upon availability to the public will be irrevocably removed upon granting of the patent;
(3) the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
(4) the deposit will be replaced if it should ever become inviable.

The deposited material, however, would not overcome the rejection against generic claims directed to mutants of AMV-RT lacking or having reduced RNaseH activity because the specification has failed to teach RNase domain and the various amino acid residues which affect its catalytic activity. Also, the specification has failed of teaching any polymerase activity for any form of the enzyme other than the homo- or heterodimeric form of AMV-RT. The enzyme is known in the prior art as homdimeric or heterodimeric. Neither the applicants or any body else taught a monomeric or trimeric, or multimeric form of AMV-RT. Finally, the application does not teach the structure of βp4-subunit of AMV-RT.

Claims 26, 28, 33, 40, 117-125 and 127-148 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrase "polymerase activity" in claims 26 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. AMV-RT is known to have both RNA-directed DNA-polymerase and DNA-directed DNA-polymerase activities. The two activities are distinct from one another because the substrates used in their assays are different and in most cases the specific activity for the RNA-directed DNA polymerase activity is much higher than the DNA-directed DNA polymerase activity. Since one of ordinary skill in the art would not know which of the polymerase activity the claims are referring to, the claims remain indefinite. While the unit of activity for the RNA-directed DNA polymerase is defined in the specification, the DNA-directed DNA polymerase activity is not defined. This rejection would be vacated if the phrase "RNA-directed DNA" is inserted before the word polymerase.
(b) and "one or more subunits" in claims 28, and 117-120 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. One or more subunit is considered indefinite because the enzymatically active form of the enzyme is a dimer and therefore there could not be more than two subunits per molecule of enzyme. For examination purposes only, "one or more subunits"

is assumed to mean homo dimer containing two α-AMV reverse transcriptase or two β-AMV reverse transcriptase; or heterodimer containing one of each the α- and β-subunits of AMV reverse transcriptase.

Applicant traverse the above rejection on the ground that there are ASLV in which each subunit has enzymatic activity.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. While some ASLV's contain monomers with RT activity, such an activity for AMV-RT has never been demonstrated by the applicants or any one else.

(c) the phrase "βp4 subunit" in claim 28, 120, and 148 is not structurally defined by the specification or the claim, and therefore, the claim is considered indefinite. For examination purposes, the phrase is interpreted as a mutant or naturally occurring allelic variants of the β-subunit which has a reverse transcriptase activity.

Applicant traverse the above rejection on the ground that βp4 subunit is defined on page 4, line 23-26, and page 56.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. Page 4, lines 23-26 teach the conversion of a 98 kDa polypeptide precursor which is converted to mature β-subunit and a p4 polypeptide. While the β-subunit of AMV-RT is well known and therefore is well defined and has enzymatic activity as a homo- and heterodimer with the α-subunit, the p4 polypeptide is not known to have any enzymatic activity as a homo- or heterodimer. This particular argument further confuses the meaning and the chemical structure of the "βp4-subunit". On page 56, the phrase AMV-RT does not appear once, and the "βp4-subunit" appears to mean the polypeptide precursor which produces the β-subunit. It is well established that α-subunit is formed from a polyprotein precursor from which the β-subunit is obtained by proteolytic cleavage. Does that make "βp4-subunit" identical to the α-subunit?

(d) All other claims not mentioned in (a)-(c) are included in these rejection because they are dependent from rejected claims and do not correct their deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26, 28, 33, 40, 117-119, 121-125 and 127-148 are rejected under 35 U.S.C. § 102(b) as being anticipated by Soltis *et al.* (see IDS: Proc. Natl. Acad. Sci. U. S. A. **1988**, 85, 3372-3376) for the reasons set forth in the previous Office action, paper number 41.

In response to the above rejections, Applicants argue that Soltis *et al.* do not teach the claimed AMV-RT.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. The polymerase activity in claim 26 from which all other claims are dependent is not defined, and therefore the rejection still valid. This rejection will be vacated if the phrase "RNA-directed DNA" is inserted before "polymerase specific activity" on line 2 of claim 26.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 26, 28, 33, 117-119, 121-125 and 127-148 are rejected under 35 U.S.C. § 103 as being unpatentable over Soltis *et al.* in view of the state of the art at the time of the application was filed.

In response to the above rejections, Applicants argue that the examiner has not established a *prima facie* case of obviousness.

Applicants' arguments filed 9/9/02 have been fully considered but they are not deemed to be persuasive. The difference between the claimed method and that tought by Soltis *et al.* is in the presumed higher specific activity of an RNA-dependent DNA polymerase activity of at least 30,000 units/mg of the produced AMV-RV. Soltis *et al.* have produce their AMV-RT by directly expressing the α- and β-subunits and purifying the recombinantly produced AMV-RT by traditional methods. The state of the art at the time of invention would have provided one of ordinary skill in the art with the knowledge, motivation, and expectation of success to improve the method taught by Soltis *et al.* The recombinant production of a desired polypeptide fused to a binding polypeptide for easy purification of said desired polypeptide is a well known method in the prior art for more than 12 years, see for example Ford *et al.* (Prot. Expr. Purif. **1991**, 2, 95-107). Ford *et al.* review the prior art of the fusion tails used for the recovery and purification of recombinant proteins that included glutathione-S-transferase (GST), *E. coli* maltose binding protein (MBP) and polyHis-tags, see Table 1. Also, they teach immobilized metal affinity chromatography using various metal ions for isolating polypeptide comprising the His-tags. In addition, they teach that fusion tails have been added to both the N- and/or C-termini of the same protein in order to isolate extremely sensitive peptide in *E. coli*. Once the fusion protein is purified by affinity chromatography, the binding peptide/protein is cleaved and separated from the desired polypeptide by various well known methods, see Ford *et al.* Thus, the ordinary skill in the art would have had the knowledge and motivation to express AMV-RT as a fusion protein, purify the fusion protein by known methods in the art, and remove the His-Tag by well known method to obtain a highly purified preparation of the enzyme. The ordinary skilled artisan would have had the expectation of success to produce the highest possible activity for the AMV-RT. It should be noted that applicants have used well known methods in the prior art at the time of invention to produce a well known enzyme. The applicants have reported or produced any unexpected results. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious, and therefore the claims remain rejected.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nashaat T. Nashed, Ph. D.
Primary Examiner